

PD

OPIC
OFFICE DE LA PROPRIÉTÉ
INTELLECTUELLE DU CANADA



Ottawa Hill K1A 0G9

CIPO
CANADIAN INTELLECTUAL
PROPERTY OFFICE

(21)	(A1)	2,150,304
(22)		1995/05/26
(43)		1995/12/01

(51) Int.Cl. ⁶ B01J 2/20; A61K 9/16

(19) (CA) APPLICATION FOR CANADIAN PATENT (12)

(54) Thermal Granulation Process

(72) Hürner, Ingrid - Germany (Federal Republic of) ;
Danz, Peter - Germany (Federal Republic of) ;
Walter, Rainhard - Germany (Federal Republic of) ;
Maasz, Joachim - U.S.A. ;
Frank, Georg - Germany (Federal Republic of) ;

(71) Bayer Aktiengesellschaft - Germany (Federal Republic of)
;

(30) (DE) P 4418837.4 1994/05/30

(57) 11 Claims

Notices: This application is as filed and may therefore contain an incomplete specification.



Industrie Canada Industry Canada

OPIC - CPO 191

Canada

2150304

Thermal granulation process

Abstract

The invention relates to a thermal process for the production of directly tabletable granules and pharmaceutical preparations produced therefrom.

La A30 264

2150304

The invention relates to a thermal process for the production of directly tabletable granules and a pharmaceutical preparation produced therefrom.

5 Direct tableting processes are preferred for the industrial production of tablets. Direct tableting means that the constituents of a tablet are pressed directly without preceding granulation processes. As a result time- and cost-consuming process steps, such as e.g. solvent removal and drying after a moist granulation, are
10 unnecessary.

High demands with respect to flowability, density, particle size etc. of their starting substances are made, however, on powder mixtures which are to be directly tabletted in order to guarantee a uniform, homogeneous
15 supply of the powder to the tablet and thus batch homogeneity. Many active compounds, such as e.g. ibuprofen and ketoprofen are unsuitable for direct tableting due to their unfavourable physicochemical properties.

20 For low-melting active compounds, i.e. for active compounds having a melting point of between 30 and 200°C, preferably between 40 and 150°C, a process has now been found to process the active compound directly to give directly tabletable granules in a simple manner together
25 with the desired customary auxiliaries.

2150304

Processes are already known from the prior art according to which tableting material is thermally treated as a preparation for direct tableting. German Offenlegungsschrift DE 3 833 448 describes a process for the production of ibuprofen preparations by direct
5 tableting. According to this process, the active compound is completely melted in a melting apparatus and then solidified and crystallized on a contact cooling apparatus. The resulting flakes of active compound are
10 ground to give a powder having improved flow properties. This ibuprofen powder can be mixed with suitable auxiliaries and then directly tableted.

EP-A 305 356 describes granules which are formed by melt granulation of a low-melting substance with its own melt.
15 As a result of the melt coating on the crystalline substance, the physicochemical properties, in particular the flow properties, are changed positively, which leads to easier tableting.

Using the processes known hitherto, only individual
20 (active) compounds are prepared for direct tableting, the other constituents of the pharmaceutical forms still having to be admixed. Depending on the nature and amount of these admixtures, the abovementioned powder technology problems which prevent or adversely affect direct tableting can again occur.
25

A further advantage of the process according to the invention lies in the fact that especially with

2150304

relatively high-dose active compounds such as, for example, ibuprofen only a small amount of auxiliaries has to be added. This leads to small pharmaceutical forms which are particularly pleasant for the consumer to take.

5 The invention relates to a thermal process for the production of directly tabletable granules, containing an active compound having a low melting point and at the same time the necessary tablet auxiliaries, which is characterized in that a mixture of active compound and
10 the necessary auxiliaries is processed by means of a melt extrusion at elevated temperature to give a homogenous non-agglutinating extrudate which is then comminuted to give tabletable granules.

The invention also relates to granules and extrudates prepared in this way and their use in the production of
15 tablets.

In the production of these granules or extrudates, the active compounds having a low melting point employed fulfil the function of a binder or of a solid solvent.
20 The granules thus obtained preferably contain 25 to 95% by weight, preferably 35 to 90% by weight, of low-melting constituents comprising active compound and auxiliaries. Low-melting active compounds which may be mentioned are preferably active substances having a melting point of
25 between 30 and 200°C, in particular of between 40 and 150°C. These include, in particular, non-steroidal analgesic substances and antiinflammatory substances of

2150304

the arylpropionic acid type. The active compounds ibuprofen, ketoprofen, naproxen and indomethacin in the form of their racemates and also as enantiomers are of particular interest.

- 5 Auxiliaries which may be mentioned are the customary tablet auxiliaries such as binders, fillers, disintegrants etc. The granules prepared according to the invention are suitable for the production of pharmaceutical preparations such as tablets, effervescent tablets, capsules, inspissated juices and dry suspensions.

- 10 Production is carried out by mixing the low-melting active compound with the suitable auxiliaries in a mixer and adding this mixture directly to a heatable extruder.
- 15 By means of the mixing and kneading elements of the extruder, the mixture is compacted to give an extrudate at a temperature at which a part of the active compound is melted. This extrudate is pressed through a perforated plate to give thin strands of 0.3 - 2.0 mm diameter and comminuted after cooling to the desired particle size of the granules. The granules thus obtained can immediately be subjected to tableting, only a lubricant, being required. By means of this process according to the invention, apart from the lubricant all auxiliaries such
- 20 as binder, disintegration auxiliaries, fillers and other auxiliaries can be incorporated directly into the granules. As a result tedious reprocessing processes become unnecessary. Since time-consuming and
- 25

2150304

environmentally polluting granulation and drying processes are likewise unnecessary, the process according to the invention is distinguished by high cost efficiency. Surprisingly, in addition to their good
5 tableting ability, the ibuprofen tablets prepared according to the invention are also distinguished by an outstanding release of the active compound as can be seen from Fig. 1. Suitable auxiliaries which may be mentioned which can be incorporated into the granules directly by
10 the process according to the invention are:
microcrystalline and microfine cellulose (Avicel and Elcema types), starch and modified starches such as rice starch or maize starch, highly disperse silica such as Aerosil, polyvinylpyrrolidones and calcium salts such as
15 e.g. calcium mono-, di- or triphosphates or calcium carbonate, as fillers, sugar alcohols such as mannitol, xylitol or sorbitol), and, as active disintegrants, crosslinked starches, crosslinked cellulose and crosslinked polyvinylpyrrolidone, and other substances
20 customary for tableting.

2150304

Exemplary embodiments

Example 1

	Substance	Mass [g]
1.	(R,S)-Ibuprofen	2000
2.	Avicel	430
3.	Aerosil	100
4.	Maize starch	390
5.	Ac-Di-Sol	60
6.	Magnesium stearate	20

5

10

The substances 1 to 5 are mixed in a tumbler mixer and then added to a heatable twin screw extruder.

The extrusion temperature is 67°C.

15

Homogeneous, non-agglutinating strands cooling in the air emerge from the die plate. These are then forcibly sieved through a 0.8 mm Frewitt sieve such that granules having a particle size between 0.05 and 0.8 mm are formed. The granules are mixed with the lubricant magnesium stearate in a tumbler mixer and then directly pressed in a suitable tablet press to give tablets of 300 mg.

C
2150304

Example 2

	Substance	Mass [g]
1.	(R,S)-Ibuprofen	2000
2.	Avicel	430
3.	Aerosil	100
5 4.	Maize starch	450
5.	Magnesium stearate	20

The extrusion of the substances 1 to 4 is carried out analogously to Example 1 and the extrusion temperature is likewise 67°C.

10 Further processing of the extrudate to give tablets having a weight of 300 mg is carried out as in Example 1.

The release characteristics of the exemplary formulations 1 and 2 are given in Figure 1.

2150304

Example 3

	Substance	Mass [g]
1.	(S)-Ibuprofen	2000
2.	Avicel	430
3.	Aerosil	100
4.	Maize starch	390
5.	Ac-Di-Sol	60
6.	Magnesium stearate	20

5

1, 2, 3 and 5 are mixed in a tumbler mixer and extruded as in Example 1.

10 The extrusion temperature is about 48°C.

After sieving through the Frewitt 0.8 mm sieve, the granules are first mixed with 4 and the lubricant 6 is then added and mixed.

15 The granules are likewise pressed to give tablets of 300 mg.

C

2150304

Example 4

	Substance	Mass [g]
1.	(R,S)-Ketoprofen	500
2.	Avicel	500
3.	Maize starch	480
4.	Magnesium stearate	20

5

10

1, 2 and 3 are mixed and extruded as indicated in Example 1, and the comminuted extrudate is mixed with the lubricant and pressed to give tablets having an intended weight of 150 mg.

The extrusion temperature is 86°C.

C

2150304

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for the production of directly tabletable granules containing an active compound having a low melting point and tablet auxiliaries, characterized in that a mixture of the active compound and tablet auxiliaries is processed directly by melt extrusion at elevated temperature of between 30 and 200°C to give a homogeneous non-agglutinating extrudate which is subsequently comminuted to give granules.
2. A process according to claim 1, characterized in that the mixture of active compound and auxiliaries employed contains 20 to 95% of low-melting constituents.
3. A process according to claim 1, characterized in that the active compound has a melting point of between about 30 and about 200°C.
4. A process according to claim 1, characterized in that the active compound has a melting point of between about 40 and about 150°C.
5. A process according to claim 1, characterized in that the active compound is a non-steroidal analgesically active compounds and/or an antiinflammatory substance of the arylpropionic acid type.

23189-7787

2150304

6. A process according to claim 1, characterized in that the active compound is ibuprofen, ketoprofen, naproxen or indomethacin.

7. A process according to claim 6, characterized in that the active compound is employed as a racemate.

8. A process according to claim 6, characterized in that the active compound is employed in enantiomerically pure form.

9. A process according to claim 1, characterized in that the (partly) molten mixture from the heatable extruder is pressed through a perforated plate to give thin strands of 0.3 to 2.0 mm diameter and these are comminuted after cooling to give granules.

10. A process according to any one of claims 1 to 9, characterized in the additional step of admixing the granules with a lubricant and tableting them.

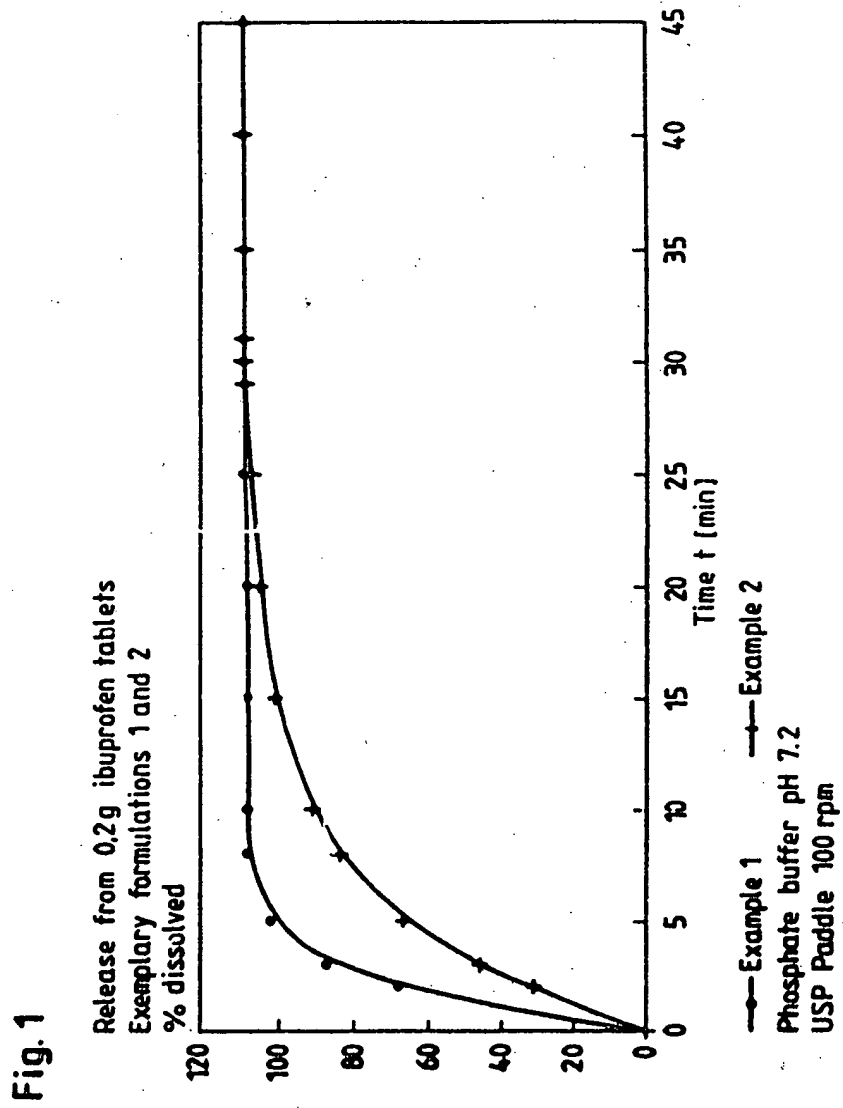
11. Use of the granules prepared according to any one of claims 1 to 9 for the production of pharmaceutical preparations.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA

PATENT AGENTS

23189-7787

2150304



Patent Agents
Fetherstonhaugh & Co.